Flavonoids as modulators of multidrug resistance

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Multidrug resistance (MDR) induced by the presence and overexpression of ATP-binding cassette transporters (ABC transporters) makes serious problems in treating of various diseases, including cancers. The orally administered drugs during the therapy are effluxed from the cells against the concentration gradient by these transporters using the energy obtained from ATP hydrolysis, thus preventing the accumulation in cells of therapeutic concentration of pharmacologically active compounds. The substrates that can be transported include lipids, sugars, amino acids, steroids, peptides, nucleotides, endogenous metabolites, ions and toxins, including antibiotics and chemotherapeutic drugs. Breast cancer resistance protein (BCRP), encoded by the ABCG2 gene is a newly identified ABC transporter, shown to confer MDR to a number of structurally and chemically unrelated compounds. It can transport both positively or negatively charged drugs, hydrophobic or hydrophilic and conjugated or unconjugated substrates. Similar to P-glycoprotein (P-gp), BCRP is also highly expressed in organs important for the absorption (the small intestine), elimination (the liver and kidney), and distribution (the blood-brain and placental barriers) of drugs and xenobiotics, it is therefore increasingly recognized for its important role in drug disposition and tissue protection. Thus, analogous to the case of P-gp, inhibitors of BCRP could be used not only to reverse MDR mediated by this transporter but also to alter the pharmacokinetics of BCRP substrate drugs, including their intestinal absorption, biliary excretion, and brain penetration, causing beneficial or adverse drug interactions. Flavonoids are biologically active polyphenolic compounds that are widely distributed in the plant kingdom. There is increasing scientific and public interests in these compounds because of their potential uses for improving human health. Several studies showed that higher utilization of flavonoids-rich dietary was associated with a lower incidence and mortality rates of diverse degenerative diseases such as cancer and cardiovascular disease. There is accumulating evidence that many of these compounds can interact with the major drug transporters (MDR-associated proteins, BCRP) in the body, leading to alterations in the pharmacokinetics of substrate drugs, and thus their efficacy and toxicity. Numerous studies demonstrated that a number of bioflavonoid interact with BCRP as substrates, inhibitors, and/or modulators of gene expression. Evidence suggests that BCRP plays a role in mediating the disposition of these compounds. In conclusion it can be noticed that since flavonoids may affect the metabolic pathways shared by many important clinical drugs, drug-flavonoid interaction is becoming a growingly significant concern. This raises consideration about the safe use of flavonoid supplements and flavonoid-containing remedies.

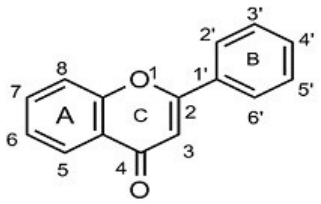

Fig. 1: Basic structure of flavonoid

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